A BACTERIAL BATTLE

The regulatory path to approving new antibiotics has been cleared, but work still remains to rebuild a **HEALTHY DRUG PIPELINE**

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BACTERIA ARE OUTSMARTING us. Every day they grow better at evading the drugs we deploy against them, and new molecular weapons are getting harder to find. The gap between our arsenal and bacteria's ability to resist it is now so wide that the World Health Organization issued a report earlier this year warning that we could soon find ourselves in a post-antibiotic era.

What would a post-antibiotic era look like? WHO cautioned that minor injuries—a cut or a scratch—could become life threatening. Medical care that we take for granted—hip replacements and bone marrow transplants—could be in jeopardy.

It sounds apocalyptic, but infectious disease specialists and drug developers have been sounding the alarm on antibiotic resistance for years. Already, doctors are helpless against infections such as drug-resistant gonorrhea. For many other bacteria, the options are dwindling. "For *Pseudomonas*, we're literally down to an antibiotic we put on the shelf 40 years ago because it was too toxic," says Glenn Tillotson, a senior partner at the life sciences consultancy TranScrip Partners.

Medical professionals are trying to prevent infections and use the remaining effective antibiotics more wisely, but new treatments are needed to replace the drugs that bacterial resistance has rendered useless. Few new antibiotic drugs have been approved in the past decade, and experts say not enough new ones are being developed to counter resistance.

From 2000 to 2014, just nine new antibiotics gained Food & Drug Administration approval; by comparison, 20 were approved from 1990 to 1999, and 43 were launched in the decade before that.

"We know that the current pipeline is not sufficient," says Helen Boucher, an infectious diseases specialist at Tufts University School of Medicine. "We need more antibiotics for gram-negative bacteria, and we also need better choices for some of our patients for gram-positive infections."

SERIOUS THREATS Graphic renditions of *Clostridium difficile* (blue), *Pseudomonas aeruginosa* (purple), *Neisseria gonorrhoeae* (orange), *Acinetobacter* (pink), and Enterobacteriaceae (yellow).

CDC/C&EN

KEY

Company
Drug candidate
Infection treated
Mode of action
● small molecule
■ monoclonal antibody
◆ peptide
◢ antibody
◀ antibody fragment

MEAGER FLOW

The antibiotics pipeline is growing but still insufficient to keep up with bacterial resistance.

PHASE I

AstraZeneca
MEDI4893
Staphylococcus
Antistaphylococcal alpha-toxin antibody ■

AstraZeneca
AZD0914
Gonococcal
Benzisoxazole DNA gyrase inhibitor ●

Basilea Pharmaceutica
BAL30072
Multi-drug-resistant gram-negative
Monosulfactam antibiotic ●

Debiopharm
AFN-1720
Staphylococcus
Prodrug inhibitor of fatty acid synthesis inhibition ●

Enanta Pharmaceuticals
EDP-788
Serious hospital
Prodrug of macrolide derivative ●

GlaxoSmithKline
GSK2696266
Bacterial
Cephalosporin ●

Medicines Co.
RPX7009/RPX2014
Multi-drug-resistant gram-negative
β-Lactamase inhibitor/carbapenem ●

Theravance
TD-1607
Gram-positive
Glycopeptide-cephalosporin heterodimer ●

PHASE II

AstraZeneca
AZD5847
Tuberculosis
Oxazolidinone ●

Cempra
CEM-102
Prosthetic joint or spacer
Fusidane ●

GlaxoSmithKline
GSK2140944
Gram-negative & gram-positive
Type II topoisomerase inhibitor ●

GlaxoSmithKline
GSK1322322
Skin & community-acquired pneumonia
Polypeptide deformylase inhibitor ●

KaloBios
KB001-A
Chronic Pseudomonas aeruginosa *airway infection in people with cystic fibrosis*
Blocks extracellular component of the bacteria's type III secretion system ◀

Melinta Therapeutics
Radezolid
Skin
Second-generation oxazolidinone ●

Merck & Co.
MK-7655
Gram-negative
β-Lactamase inhibitor ●

Veterans of antibiotics development point to three major fronts where battles need to be won in order to refill the antibiotics medicine chest: clear and reasonable expectations from regulatory authorities on the data needed to approve an antibiotic, better approaches by researchers to finding new treatments for bacterial infections, and a willingness by the public to value new antibiotics in a way that rewards innovation.

Advances, although incremental, are being made on all three fronts to push molecules through the clinic and onto the market. After a lengthy new-drug drought, Durata Therapeutics' dalbavancin was approved last month, and another four antibiotics could be on the market in the next year.

MOST OF THE PROGRESS has been regulatory. Not long ago, antibiotics developers felt stymied by FDA's requirements. One of the biggest gripes was that the agency had unrealistic expectations for how much data should be collected to win its approval.

"If you followed some of the guidance to the letter as it was written for some of the critical indications where new antibiotics were needed, you would have had to run enormous clinical trials," says David Payne, head of GlaxoSmithKline's antibacterials discovery unit. "It would take many years to finish, when the unmet medical need is here, right now, today."

Dalbavancin's long road to approval highlights the regulatory hurdles that prompted many drug firms to abandon antibiotics. Discovered in 1996, dalbavancin took 18 years to win FDA's green light. In that time it went through multiple owners that conducted five Phase III studies—the last stage of testing before approval—involving nearly 3,000 people overall.

"It spent a lot of time languishing," says Michael W. Dunne, Durata's chief medical officer. Dunne previously led the infectious disease development group at Pfizer, which sold the dalbavancin program to Durata in 2009. The problem for antibiotic development at the time, Dunne recalls, was that companies would spend years recruiting for and conducting large Phase III studies, only to find when they finished that the regulatory guidelines had changed.

The same year that Durata bought dalbavancin, two other antibiotics on the cusp of approval were on the losing side of a regulatory review. "It was probably a low point," says Guy Macdonald, chief executive officer of Tetraphase, a biotech firm developing tetracycline derivatives.

The tide began to turn in July 2012, when Congress passed legislation creating incentives for antibiotic development while requiring FDA to clear a wider pathway for their approval. In addition to extending by five years the patent life on some new antibiotics, the act, Generating Antibiotic Incentives Now (GAIN), required FDA to set guidelines for smaller, more focused clinical trials.

To address the challenges, FDA borrowed some of the strategies it had been using to facilitate development of drugs for orphan diseases. Like some bacterial infections, orphan diseases have small patient populations that make it difficult to conduct sizable studies with traditional goals.

In an important change of mind-set, regulators now acknowledge that antibiotic developers face a paradox, says John Rex, head of infection at AstraZeneca. Recruiting enough patients for a large Phase III trial of an antibiotic is in some cases impossible "until the epidemic is already upon us," Rex says. By then it's too late.

NOW, FDA acknowledges that, unlike in most therapeutic areas, preclinical models of an antibiotic's efficacy are fairly good predictors. When an antibiotic kills bacteria in a mouse, scientists can be confident it will do the same thing in humans, Rex says. Of course, safety still has to be demonstrated.

As such, FDA is allowing companies to conduct smaller studies in areas of high unmet need; in some instances it will allow data from studies of different types of infection to be combined. "A lot of work has been to try and address the issues of practical feasibility of conducting clinical trials of new antibacterial drugs while still maintaining trials that are scientifically sound," says Edward M. Cox, director of FDA's Office of Antimicrobial Products.

GAIN also introduced special incentives for companies developing qualified infectious disease products (QIDPs)—antibacterials addressing serious or life-threatening infections. FDA is required to speed up its review of those products, and, once approved, drugs with QIDP status earn an extra five years of market exclusivity. That additional time is tacked on to any years gained from other special statuses,

PHASE III

MerLion Pharmaceuticals
Finafloxacin
Urinary tract
Fluoroquinolone ●

Novartis
LFF571
Clostridium difficile
Elongation factor inhibitor ●

Roche
POL7080
Pseudomonas
Synthetic cyclopeptide ●

Summit
SMT 19969
C. difficile
Not disclosed ●

Achaogen
Plazomicin
Carbapenem-resistant Enterobacteriaceae
Semisynthetic aminoglycoside ●

Actelion
Cadazolid
C. difficile-*associated diarrhea*
Inhibitor of *C. difficile* protein synthesis ●

AstraZeneca
CAZ-AVI
Urinary tract
β-Lactamase inhibitor ●

Basilea Pharmaceutica
Ceftobiprole
Gram-negative & gram-positive
Cephalosporin ●

Cempra
Solithromycin
Community-acquired bacterial pneumonia
Fluoroketolide ●

Cubist Pharmaceuticals
Surotomycin
C. difficile-*associated diarrhea*
Antibacterial lipopeptide ◆

Melinta Therapeutics
Delafloxacin
Skin
Fluoroquinolone ●

Merck & Co.
MK-3415 & *MK-6072*
C. difficile
Antibody targeting *C. difficile* toxins A & B ◢

Tetraphase Pharmaceuticals
Eravacycline
Multi-drug-resistant bacteria
Tetracycline derivative ●

UNDER FDA REVIEW

Cubist Pharmaceuticals
Tedizolid phosphate
Gram-positive
Oxazolidinone ●

Medicines Co.
Oritavancin
Skin
Lipoglycopeptide ◆

Cubist Pharmaceuticals
Ceftolozane/tazobactam
Urinary tract
Cell wall synthesis inhibitor/ β-lactamase inhibitor ●

SOURCES: Companies, ClinicalTrials.gov

such as orphan drug designation or pediatric exclusivity.

Companies are swiftly moving to take advantage of the new incentives. As of June 4, FDA has granted 46 QIDP designations across 32 chemical entities, according to the agency. Durata's dalbavancin, now known by the brand name Dalvance, was the first QIDP-designated drug to reach the market.

GAIN also required FDA to figure out a path for approving antibacterials against specific pathogens, such as *Pseudomonas*. Currently, when an antibiotic gets FDA's nod, the product label is for a specific indication—skin infection, for example—and FDA doesn't allow it to be promoted for other indications that involve the same pathogen. A company needs to conduct separate tests to expand the drug's label.

Under the proposed pathway, certain products—say a narrow-spectrum antibiotic or an antibody that targets a single pathogen—could offer up a smaller set of data to secure a product label for a particular bug.

In theory, the pathogen-specific pathway should lead to smaller and faster studies, advantages that helped to lure Roche back into the antibiotics business, says Janet Hammond, head of the company's infectious diseases translational unit. After a lengthy hiatus from antibiotics R&D, Roche recently reentered the field through a series of collaborations.

IN NOVEMBER, Roche licensed POL7080, a macrocycle in Phase II studies for the treatment of *Pseudomonas* infections, from the Swiss biotech firm Polyphor. Under the pathogen-specific pathway, the door is open for companies to run much smaller trials: A narrow-spectrum drug could in theory be approved based on a 300-person study that looks at its efficacy in many situations—say, intra-abdominal infections, pneumonia, and skin infections.

The pathogen-specific pathway is important to Roche, according to Hammond, because it enables the firm to develop antibiotics in a cost-efficient way. Patients are the biggest beneficiaries, she adds, because POL7080 could represent the first new class of agents to be developed for gram-negative bacteria in 30 years.

Not everyone is convinced all the kinks have been worked out of the single-pathogen strategy. Recruiting 300 people to test a drug against certain bacteria—the rare but deadly *Acinetobacter,* for example—will still take a long time, Tetraphase's Macdonald notes.

The guidelines for approval of single-pathogen and other limited-spectrum drugs are in draft form, but the goal is to recognize some of the practical realities of antibiotic development, FDA's Cox says. "If you've got a serious infection, and you don't have much in the way of options, that has a major impact on risk analysis."

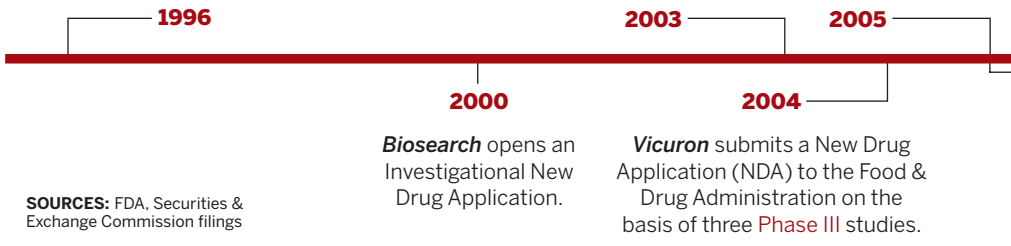
The single-pathogen pathway is one of several improvements that could be made in the regulatory process, industry executives say. Another is that FDA and European regulators should get on the same page about what they want out of studies. "There's a need for genuine global harmonization," GSK's Payne says. For example, regulators around the world still have different attitudes about what a smaller development pathway means.

Although a straighter regulatory path should help more antibiotics reach the market, many in the business are worried that not enough early-stage research is being done to sustain even the slow trickle of the current pipeline. The number of big pharma companies active in antibiotics has dwindled from 18 in 1990 to just a handful today.

Some small and medium-sized biotech firms are active, but most of their compounds are derivatives of existing therapeutic classes. And although doctors welcome any potent new antibacterial, the need for new and better mechanisms of action is great.

The problem with derivatives of earlier drugs, Durata's Dunne notes, is that it gets sequentially harder to find better versions. "There's nothing wrong with improving on a chemical substrate that works so far," Dunne says. "But when you do that, the next generation has to be able to address the liabilities created by the previous generation." That's because each iteration on the first anti-infective prompts bacteria to come up with more ways to avoid the class's killing power.

A LONG ROAD Dalbavancin faced many setbacks in its 18-year road to approval.



SOURCES: FDA, Securities & Exchange Commission filings

BUT FINDING ANTIBIOTICS that work in new ways is tough. The first decades of antibiotics drug discovery were focused on the molecules that microorganisms make themselves to combat their bacterial brethren. But bacteria can only be coaxed to produce so many novel molecules in an unnatural setting—a petri dish—and after a period of bountiful discoveries, researchers started to find the same antibiotics over and over again.

In the mid-1990s, many big pharma firms switched to target-based screens and rational drug design. The results were abysmal: A now infamous study by GSK's Payne showed that seven years of GSK effort—including 70 large screening campaigns to find small-molecule antibiotics acting by new mechanisms of action—produced just five "hits."

The biotech and pharma companies that have stayed in the game maintain that they

are taking a smarter approach to finding novel antibiotics. "Microbiology is very different now from when most companies exited the space," Roche's Hammond says.

As she notes, scientists have sequenced the genomes of various bacteria and understand better how bacteria communicate with one another. That information "should allow a whole new variety of opportunities for us," including new molecules and mechanisms of action, Hammond says.

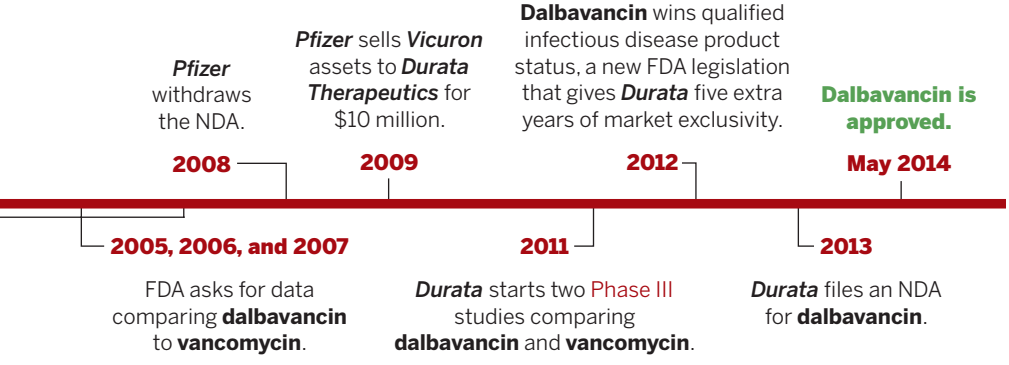
For example, antibodies could provide a workaround for the bacterial resistance that eventually renders small-molecule antibiotics useless. Broad-spectrum antibiotics expose both bad and good bugs to a drug, and resistant bacteria are left behind to flourish. Antibodies, on the other hand, are selective. If they work right, they should target only the bad bacteria, preserving the healthy microbiome.

But developing an antibody to treat a bacterial infection is not without its hurdles. "Bacteria and viruses are very variable, and finding antibodies that have the breadth of activity you need for a particular pathogen or group of pathogens that you're interested in treating can be technically challenging," says Daria Hazuda, head of infectious disease discovery efforts at Merck & Co.

For that reason, many companies are not targeting the antibody directly at the pathogen. Instead, they are focusing on neutralizing bacterial toxins, which damage tissue and prevent the immune system from sweeping away the bad bugs. Merck has one of the most advanced programs: a pair of antibodies that neutralize two toxins produced by *Clostridium difficile*.

In some cases, antibodies could be used prophylactically to prevent an infection—an approach that isn't possible with small-molecule drugs because of resistance concerns. The idea is to identify and treat people with a high risk for known resistant infections, such as hospitalized patients on a ventilator or people with cystic fibrosis, whose lungs are chronically colonized with *Pseudomonas*.

Roughly 25% of patients on a ventilator are colonized with *Staphylococcus aureus*, and at least a quarter of those people will go on to develop pneumonia, explains Eszter Nagy, president of Arsanis Biosciences, a biotech firm developing antibacterial antibodies. Preventing pneumonia in those patients would save lives as well as the expense of extra days in the hospital. "It's easier to prevent an infectious disease than to treat it," Nagy says.



ANTIBODIES HAVE PROMISE, but industry veterans say small molecules will continue to be a cornerstone of anti-infective treatment. Although Merck has antibodies in late-stage development, the company's discovery programs are squarely focused on finding small molecules. Merck is using tried-and-true empirical screening methods, "but doing it in a way that hasn't been done before," Hazuda says. The idea is to screen smarter by using the information gleaned from genetic sequencing and the firm's improved understanding of biological pathways.

Given how hard it is to find novel anti-infectives, companies and infectious disease experts alike say more incentives need to be introduced to keep R&D alive.

Public-private partnerships are helping to sustain early research, including at some big pharma firms, but everyone agrees the promise of better pricing is what will really keep companies in the field. To keep spending on antibiotics R&D, drugmakers need to know they will get a return on their investment. For that to happen, "a sea

change in public perception of the value of antibiotics" needs to occur, TranScrip's Tillotson says.

"Antibiotic drugs are one of the few classes that can actually stop you from dying," Tillotson says, and yet, many patients and insurers are unwilling to pay a premium for a short course of antibiotics that could save a person's life.

The perks established through GAIN are great, but "there's still room to go with incentives on the commercial side," Durata's Dunne adds. As he points out, some of the most expensive oncology drugs cost upward of $100,000 and extend life for only a few months. And yet, many hospitals balk at paying several thousand dollars for a short course of antibiotics that could save a life.

"Society needs to stand up and say it's worth those five-figure-type costs to solve this problem that at the moment is looking unsolvable," Dunne says.

Part of the quandary is that the pharmaceutical industry's conventional business model—trying to sell as much of a drug as possible—can't be applied to antibiotics. A company that pushes use of its new antibiotic over older, still-effective drugs is in effect encouraging resistance to its drug. In no other markets are companies asked to be good stewards by withholding their drugs.

Although the five years of exclusivity given to QIDP products is great, it does not go far enough, Dunne argues. To encourage companies to promote new antibiotics judiciously, he suggests offering additional exclusivity to companies that are responsible stewards during the first 10 years a drug is on the market.

Efforts are being made to bridge the gap between the public's perception of an antibiotic's worth and what a drug developer needs to charge. For example, New Drugs for Bad Bugs, established by the European public-private partnership Innovative Medicines Initiative, is bringing stakeholders together to find ways to pay for antibiotics that reward innovation.

"THE GOAL is to come up with a collection of different ideas that can be tested," AstraZeneca's Rex says, acknowledging that what works in one country might not be appropriate for another.

Industry experts are encouraged that a conversation is starting about what new antibiotics are worth. Many were surprised by the open dialogue between industry, academics, and payers at an antibiotics conference sponsored last year by the Pew Charitable Trusts. And a working group established by London's Chatham House, a nonprofit policy institute, is exploring how to ensure that the value of antibiotics is not a function of how much is sold.

Taken together, the efforts are encouraging, but antibiotic experts caution that they still aren't enough to win the bacterial battle. An optimist, Tufts's Boucher thinks that efforts to prevent infection, better stewardship of antibiotic use, and new drug options should be enough to keep catastrophic bacterial outbreaks at bay.

But Boucher also knows her more pessimistic colleagues worry that, in five years' time, doctors will have to think carefully before performing now-common procedures. "Nobody wants that," she says. ■